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ORIGINAL ARTICLE

Secondary cancers after a childhood cancer diagnosis: a nationwide hospital-based retrospective cohort study in Japan

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Abstract

Background The epidemiology of secondary cancers in childhood cancer survivors has been unknown in Asian countries. Our aim is to assess the incidence and risk factors for secondary cancers through a nationwide survey in Japan.

Methods A retrospective cohort study comprising 10,069 children who were diagnosed with cancer between 1980 and 2009 was conducted in 15 Japanese hospitals. The cumulative incidence rate was calculated using death as the competing risk and compared by the Gray method. The standardized incidence ratio (SIR) was defined as the ratio of the number of observed cancers divided by the number of expected cancers. The risk factors were analyzed using Cox regression analysis.

Results One hundred and twenty-eight patients (1.3 %) developed secondary cancers within a median follow-up of 8.4 years. The cumulative incidence rate was 1.1 % (95 % confidence interval [CI] 0.9–1.4) at 10 years and 2.6 % (95 % CI 2.1–3.3) at 20 years after primary cancer diagnosis. Sensitivity analysis, limited to 5-year survivors (n = 5,387), confirmed these low incidence rates. The SIR of secondary cancers was 12.1 (95 % CI 10.1–14.4). In the

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Cox analysis, the hazard ratios for secondary cancers were 3.81 (95 % CI 1.53–9.47) for retinoblastoma, 2.78 (95 % CI 1.44–5.38) for bone/soft tissue sarcomas, and 1.81 (95 % CI 1.16–2.83) for allogeneic stem cell transplantation.
Conclusions The cumulative incidence of secondary cancers in children in Japan was not high; however, the SIR was relatively high. Retinoblastoma or sarcoma in addition to allogeneic stem cell transplantation were significant risk factors for secondary cancers.

Keywords Secondary cancers · Childhood cancer · Cumulative incidence · Standardized incidence ratio · Risk factors

Abbreviations

SIR	Standardized incidence ratio
CI	Confidence interval
CCSS	Childhood Cancer Survivor Study
BCCSS	British Childhood Cancer Survivor Study
AML	Acute myeloid leukemia
MDS	Myelodysplastic syndrome
AER	Absolute excess risk
ALL	Acute lymphoblastic leukemia
CML	Chronic myeloid leukemia
NHL	Non-Hodgkin's lymphoma
PNET	Primitive neuroectodermal tumor
HR	Hazard ratio
OS	Overall survival
OR	Odds ratio

Introduction

The recent increase in multidisciplinary therapy has steadily improved the cure rate of children with cancer. However, the immunosuppressive and cytotoxic treatment necessary to achieve this improvement has increased the risk of subsequent late effects [1, 2], including the development of secondary cancer, which is considered one of the most serious and life-threatening late effects [3–6].

Reports from previous studies [7, 8], including the Childhood Cancer Survivor Study (CCSS) [3, 9] and British CCSS (BCCSS) [10, 11], have contributed important evidence regarding the risk of subsequent primary neoplasms among survivors of childhood cancers. However, the study populations in both of these large cohorts were childhood cancer patients who survived at least 5 years after the primary cancer diagnosis, and the results do not account for the time at risk during the first 5 years [12, 13]. While the majority of secondary cancers develop ≥5 years after primary cancer diagnosis, some secondary cancers, such as acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) occur within the first 5 years [8, 14, 15].

The current study aimed to determine the incidence and risk factors for secondary cancers in children with any primary malignancy who had survived ≥2 months after diagnosis through a nationwide survey in Japan. To the best of our knowledge, this is the first report from an Asian country to describe the epidemiology of secondary cancers in survivors of any kind of childhood cancers.

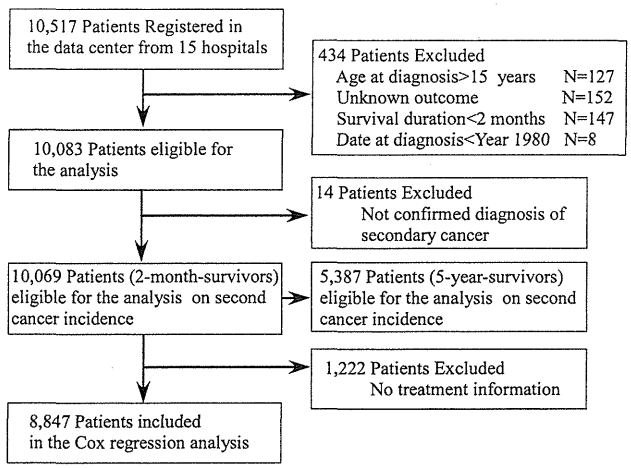

Fig. 1 Study flow diagram describing the criteria for patient selection to determine the incidence and risk factors for secondary cancer in pediatric cancer patients

Materials and methods

Study population

The target study population included 10,517 children who were newly diagnosed with cancer in 15 hospitals in Japan between 1980 and 2009. Patients included in the analysis were <16 years at the time of primary cancer diagnosis, survived ≥2 months after diagnosis, and had outcome information available (n = 10,069; 2-month survivors, Fig. 1). We were unable to obtain detailed treatment information such as irradiation dose or cumulative dose of anticancer drugs from two of the participating hospitals. Cox regression analysis was conducted on 8,847 patients, excluding patients without treatment information (n = 1,226), to evaluate the risk factors for secondary cancers (Fig. 1).

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Follow-up and data collection

The diagnostic and treatment data for primary cancers were documented from 15 participating hospitals listed in the acknowledgment section. We administered a survey via the treating hospitals to collect the following data regarding secondary cancer diagnosis—date of diagnosis, cytological or histological reports including cytogenetic findings, cancer site, cumulative treatment exposure before secondary cancers, and outcomes. The time at risk for secondary cancers was computed from the date of primary cancer diagnosis to the date of secondary cancer diagnosis, date at time of death, or date of last contact, whichever came first. Age at diagnosis and last-follow-up, and incubation time to secondary cancer were all calculated as real numbers in days divided by 365.25 and rounded duly. The end of the follow-up period was March 31, 2010.

Statistical analysis

The cumulative incidence of secondary cancers over time was calculated using competing risk methods (considering any death as a competing event) [16]. To evaluate immortal time bias, we compared the cumulative incidences of secondary cancers between 2-month survivors and 5-year survivors (patients who had survived >5 years after primary cancer diagnosis (n = 5,387; Fig. 1) as a sensitivity analysis. The incidence rates of cancer in the Japanese general population were obtained from the regional cancer registry of the National Cancer Center Hospital in Japan [17, 18] and used to calculate the number of cancers expected to occur in the patient cohort by calculating the total person-years at risk by sex and 5-year age groups and multiplying by the corresponding cancer rates observed in the general population. The standardized incidence ratio (SIR), defined as the ratio of the number of observed cancers divided by the number of expected cancers, was used to evaluate the difference in cancer occurrence between the childhood cancer survivors and the general population. Absolute excess risk (AER) was calculated as the difference between the number of observed and expected events divided by the number of person-years of follow-up and was expressed per 100,000 person-years.

Primary cancers were classified into 6 major categories—hematological malignancies (acute lymphoblastic leukemia [ALL], AML, MDS, chronic myeloid leukemia [CML], non-Hodgkin's lymphoma [NHL], Hodgkin's lymphoma, and other leukemias), retinoblastoma, pediatric solid tumor (neuroblastoma, hepatoblastoma, nephroblastoma [Wilms tumor], and germ cell tumors), brain tumors, bone/soft tissue sarcoma (osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, and other sarcomas), and others (Langerhans cell histiocytosis, adult-type carcinoma, and others).

Secondary cancers were also classified into 6 major categories—hematological malignancies (ALL, AML, MDS, and NHL), brain tumors (meningioma, glioma, primitive neuroectodermal tumor [PNET], and germ cell tumor), thyroid cancer, adult-type carcinoma (renal cancer, breast cancer, oral cancer, gastrointestinal cancer, lung cancer, and cervical/ovarian cancer), sarcoma (osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma), and neurogenic tumors (malignant schwannoma and abdominal PNET).

Survival analysis was conducted using Kaplan–Meier methods (log-rank method for comparison) and the Cox regression model for hazard ratio (HR) estimates. Variables examined in the regression model included age at primary cancer diagnosis, attained age at last follow-up, surgery, radiation, and stem cell transplantation. Age at cancer diagnosis was analyzed as a categorical variable by tertile ($\leq$2.00 years, 2.01–6.00 years, and $\geq$6.01 years). Attained age at last follow-up was also analyzed as a categorical variable by tertile ($\leq$9.00 years, 9.01–16.00 years, and $\geq$16.01 years). Data were analyzed using SPSS version 22.0 (IBM Japan Ltd., Tokyo, Japan) and EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [19]. More precisely, it is a modified version of R commander designed to conduct statistical functions frequently used in biostatistics [19].

Results

Patient characteristics for the 2-month and 5-year survivors are shown in Table 1. The age at diagnosis of primary cancer was significantly older in 2-month survivors than in 5-year survivors ($p < 0.001$), but the age at the final observation was significantly younger in 2-month survivors than in 5-year survivors ($p < 0.001$). The proportion of each primary cancer type was similar between the 2 groups; however, 5-year survivors experienced significantly more ALL ($p = 0.008$) and neuroblastoma ($p = 0.021$), and 2-month survivors experienced significantly more AML ($p = 0.004$), MDS ($p = 0.014$), brain tumor ($p < 0.001$), and rhabdomyosarcoma ($p = 0.027$). Most survivors had received chemotherapy, less than half of the survivors had received surgery and/or radiation. The overall survival (OS) for each of the 6 cancer types in 2-month survivors is illustrated in Supplemental Fig. 1. The 10- and 20-year OS rates of 2-month survivors were 69.0 and 66.2 %, respectively. The 10-year OS ranged from 55.3 % (brain tumors) to 90.0 % (retinoblastoma).

The median follow-up duration after primary cancer diagnosis was 8.4 years (range 0.2–30 years) in 2-month

Table 1 Comparison of pediatric cancer patient characteristics between those who survived at least 2 months and those who survived at least 5 years

	2-month survivors ($n = 10,069$)	5-year survivors ($n = 5387$)	p value
Sex (boys)	5,708 (56.7)	3,047 (56.6)	0.936
Age at diagnosis of primary cancer (years)	5.80 ± 4.6 (4.6)	5.40 ± 4.5 (4.1)	<0.001
≤2 years	3,723 (37.0)	2,152 (39.9)	0.015
3–6 years	2,708 (26.9)	1,503 (27.9)	0.312
≥7 years	3,638 (36.1)	1,732 (32.2)	0.001
Age at last follow-up (years)	13.5 ± 7.8 (12.6)	17.9 ± 7.1 (17.6)	<0.001
Primary cancer			
Acute lymphoblastic leukemia (ALL)	3,199 (31.2)	1,870 (34.7)	0.008
Acute myeloid leukemia (AML)	1,177 (11.7)	537 (10.0)	0.004
Myelodysplastic syndrome (MDS)	194 (1.9)	74 (1.4)	0.014
Chronic myeloid leukemia (CML)	136 (1.4)	66 (1.2)	0.518
Non-Hodgkin lymphoma (NHL)	783 (7.8)	439 (8.2)	0.450
Hodgkin lymphoma (HL)	94 (0.9)	65 (1.2)	0.113
Brain tumor	668 (6.6)	262 (4.9)	<0.001
Neuroblastoma	1,406 (14.0)	838 (15.6)	0.021
Retinoblastoma	223 (2.2)	129 (2.4)	0.485
Hepatoblastoma	219 (2.2)	112 (2.1)	0.701
Nephroblastoma (Wilms tumor)	315 (3.1)	192 (3.6)	0.161
Osteosarcoma	211 (2.1)	86 (1.6)	0.034
Ewing sarcoma	143 (1.4)	61 (1.1)	0.140
Rhabdomyosarcoma	326 (3.3)	139 (2.6)	0.027
Germ cell tumor	328 (3.3)	177 (3.3)	0.928
Langerhans cell histiocytosis	247 (2.5)	131 (2.4)	0.936
Other leukemia	54 (0.5)	14 (0.3)	0.014
Other sarcoma	112 (1.1)	55 (1.0)	0.605
Adult-type carcinoma	48 (0.5)	28 (0.5)	0.717
Others	237 (2.4)	108 (2.0)	0.171
Therapy			
Chemotherapy	7,817 (90.4)	4,240 (91.2)	0.590
Surgery	3,217 (37.2)	1,709 (36.7)	0.837
Radiation	3,594 (41.6)	1,878 (40.4)	0.476
Allogeneic stem cell transplantation	1,479 (17.1)	686 (14.7)	0.004
Autologous stem cell transplantation	882 (10.2)	425 (9.1)	0.088
Secondary cancers	128 (1.3)	100 (1.9)	0.005
Mortality rate	2,785 (27.7)	362 (6.7)	<0.001

Data are presented as n (%) or mean ± standard deviation (median)

survivors and 11.2 years (range 5.0–30 years) in 5-year survivors, respectively. Total follow-up duration was 77,151 person-years. As of 31 March 2010, a total of 128 secondary cancers were diagnosed, including AML ($n = 29$), MDS ($n = 22$), adult-type carcinomas ($n = 19$), brain tumors ($n = 18$), bone/soft tissue sarcoma ($n = 16$), thyroid cancer ($n = 12$), ALL ($n = 5$), NHL ($n = 2$), and neurogenic tumors ($n = 5$) in 2-month survivors. Forty-two secondary hematological cancers (23 AML, 14 MDS, 4 ALL, 1 NHL) developed during the first 5 years after primary cancer diagnosis (42/58; 72 %), while other types of secondary cancers were relatively rare within the 5-year period (<6 %).

Cumulative incidence

The overall cumulative incidence of secondary cancers in 2-month survivors was 1.1 % (95 % confidence interval [CI] 0.9–1.4) at 10 years and 2.6 % (95 % CI 2.1–3.3) at 20 years from the time of primary cancer diagnosis

(Fig. 2a). The corresponding cumulative incidence in 5-year survivors with secondary cancer within 5 years was 1.2 % (95 % CI 0.9–1.5) at 10 years and 3.2 % (95 % CI 2.4–4.1) at 20 years from the time of primary cancer diagnosis (Fig. 2b). The cumulative incidence in 5-year survivors without secondary cancer within 5 years was 0.7 % (95 % CI 0.5–1.0) at 10 years and 2.7 % (95 % CI 2.0–3.6) at 20 years from the time of primary cancer diagnosis (Fig. 2c).

Clinical characteristics of secondary cancers

The clinical characteristics of the patients with secondary cancers are summarized in Table 2, according to the 6 categories of secondary cancers. More girls (67 %) were diagnosed with secondary thyroid cancers, while more boys were diagnosed with secondary bone/soft tissue sarcoma (69 %) or neurogenic tumor (80 %). The secondary cancer types correlated well with the primary cancer types. Bone/soft tissue sarcoma developed in 5 out of 6 patients with retinoblastoma. Most secondary brain tumors developed in survivors with hematological malignancies or brain tumors. Many secondary thyroid cancers and adult-type carcinomas developed in survivors with hematological malignancies or solid tumors. Secondary hematological malignancies developed in all primary cancer groups except retinoblastoma alone.

The median incubation time from primary cancer diagnosis to secondary cancer was 6 years (range 1–27 years) and varied according to the type of secondary cancer (Table 2; Fig. 3a). The median time to diagnosis was shortest with hematological cancers (median 3.0 years) and longest with adult-type carcinoma (median 15 years). Hematological cancers developed earliest (during the first 5 years after primary cancer diagnosis) while other types of secondary cancers were relatively rare within the 5-year period (Fig. 3b), which corresponded with an age at diagnosis that was younger than the other cancer types (Table 2).

With regard to characteristics related to the treatment of primary cancers, the highest proportion of patients underwent cranial irradiation (CRT) for secondary brain and neurogenic tumors, while non-CRT irradiation occurred most frequently with thyroid cancer (90 %). Of the 1,466 allogeneic stem cell transplantations (SCT) performed for primary cancers, 33 patients developed secondary cancer (crude odds ratio [OR] 1.66; 95 % CI 1.17–2.34) and received total body irradiation-containing conditioning regimens. Tongue carcinoma developed in 2 of these 3 patients during chronic graft-versus-host disease after allogeneic SCT.

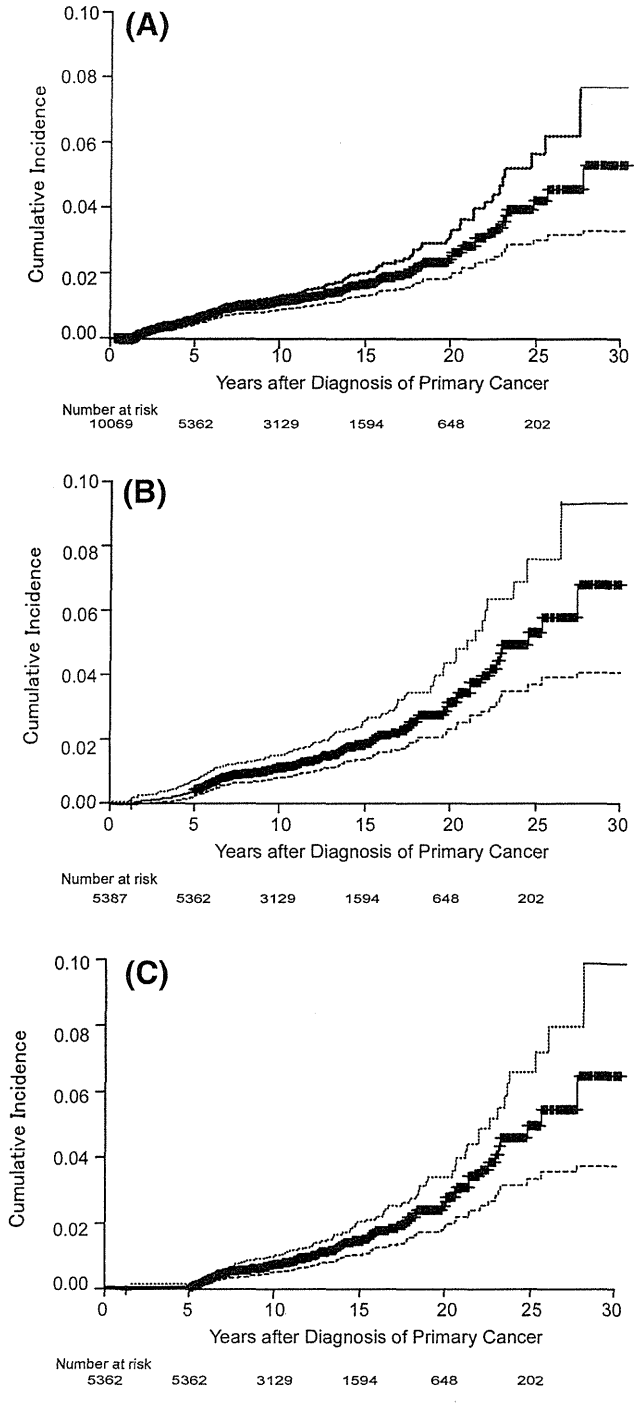

Fig. 2 Cumulative incidence of secondary cancers in pediatric patients with any type of primary cancer. The cumulative incidence of secondary cancers as a function of time after primary cancer diagnosis over a maximum follow-up of 30 years. The *dotted lines* represent the 95 CI, and the *thick lines* represent the censored patients. **a** The overall cumulative incidence of secondary cancers in the 2-month survivors, **b** the cumulative incidence in 5-year survivors including those who developed secondary cancer within 5 years, and **c** the cumulative incidence in 5-year survivors who did not develop secondary cancer within 5 years

Table 2 Clinical characteristics of patients with secondary cancers

	Total	Hematological malignancy	Brain tumor	Thyroid cancer	Adult-type carcinoma	Bone/soft tissue sarcoma	Neurogenic tumor
2-month suvivors							
Total number	128	58	18	12	19	16	5
Sex (male:female)	66:62	29:29	8:10	4:8	10:9	11:5	4:1
Primary cancer							
Age at diagnosis of primary cancer	6.2 ± 4.5 (5)	6.9 ± 5.3 (6)	7.6 ± 4.5 (6)	4.8 ± 5.0 (3)	7.3 ± 4.9 (5)	3.9 ± 4.4 (2)	6.2 ± 4.9 (3)
Hematological malignancy	61 (48)	25 (41)	13 (21)	4 (7)	8 (13)	6 (10)	5 (8)
Retinoblastoma	7 (5)	1 (14)	0	0	0	6 (86)	0
Pediatric solid tumor	30 (23)	15 (50)	2 (7)	4 (13)	8 (27)	1 (3)	0
Brain tumor	8 (6)	3 (38)	3 (38)	1 (12)	0	1 (12)	0
Bone/soft tissue sarcoma	16 (13)	10 (63)	0	2 (12)	2 (12)	2 (12)	0
Others	6 (5)	4 (67)	0	1 (17)	1 (17)	0	0
Secondary cancer (SC)							
Incubation time to SC (years)	8.7 ± 6.8 (6)	4.0 ± 3.1 (3)	11.1 ± 6.2 (11)	12.9 ± 6.4 (13)	15.7 ± 7.2 (15)	9.4 ± 5.9 (7.5)	14.4 ± 6.4 (17)
Age at diagnosis of SC (years)	14.9 ± 7.9 (14)	10.9 ± 5.7 (10)	18.7 ± 7.9 (17)	17.6 ± 7.3 (18)	23.0 ± 7.8 (23)	13.3 ± 7.4 (12)	20.6 ± 9.5 (23)
Age at last follow-up (years)	18.4 ± 8.9 (17)	14.2 ± 7.5 (13)	22.9 ± 8.9 (24)	23.3 ± 8.2 (23)	26.3 ± 8.2 (27)	17.6 ± 8.1 (15)	23.7 ± 11.5 (24)
Sub-classification	N/A	AML (29)	Meningioma (7)	Papillary (6)	Renal cancer (5)	Osteosarcoma (10)	Malignant schwannoma (5)
		MDS (22)	Glioma (6)	Follicular (6)	Breast cancer (3)	Ewing sarcoma (4)	
		ALL (5)	PNET (4)		GI cancer (4)	Rhabdomyosarcoma	
		NHL (2)	Germ cell tumor (1)		Oral cancer (3)	Sarcoma (2)	
					Lung cancer (2)		
					Cervical cancer (1)		
					Ovarian cancer (1)		
Treatment for primary cancer							
Cranial irradiation (CRT)	42/120 (35)	12/56 (21)	11/16 (69)	4/11 (36)	5/18 (28)	6/15 (40)	4/4 (100)
Dose of CRT (Gy)	12–56	18–41	18–50	24–56	18–24	15–24	12–24
Other irradiation	51/117 (44)	17/56 (30)	5/16 (31)	10/11 (90)	9/15 (60)	9/15 (60)	1/4 (25)
Anthracyclines (DOX ≧ 250 mg/m^2)	44/111 (40)	17/49 (35)	7/16 (44)	2/10 (20)	11/17 (65)	7/15 (47)	0/4 (0)
Cyclophosphamide (≧5 g/m^2)	56/107 (52)	22/51 (43)	9/15 (60)	6/10 (60)	11/17 (65)	6/10 (40)	2/4 (50)
Etoposide (≧3 g/m^2)	19/112 (17)	9/51 (18)	4/15 (27)	2/10 (20)	1/17 (6)	3/15 (20)	0/4 (0)
Cis-platinum (≧300 mg/m^2)	39/123 (32)	19/51 (37)	4/16 (25)	3/10 (30)	6/17 (35)	7/15 (47)	0/4 (0)

Table 2 continued

	Total	Hematological malignancy	Brain tumor	Thyroid cancer	Adult-type carcinoma	Bone/soft tissue sarcoma	Neurogenic tumor
Allogeneic stem cell transplantation	29/128 (23)	17/58 (29)	3/18 (17)	3/12 (25)	2/19 (11)	2/16 (13)	2/5 (40)
Autologous stem cell transplantation	24/128 (19)	14/58 (24)	0/18 (0)	2/12 (17)	2/19 (11)	5/16 (31)	1/5 (20)
Standardized incidence ratio (SIR) and absolute excess risk (AER)							
Number observed/expected	128/10.6	58/2.77	18/1.34	12/0.46	19/2.55	21/2.73	
SIR (95 % CI)	12.1 (10.1–14.4)	20.9 (15.9–27.1)	13.4 (7.96–21.2)	26.0 (13.4–45.6)	7.45 (4.49–11.6)	7.69 (4.76–11.8)	
AER/100,000 person-year	306.3	139.7	44.5	31.6	42.7	45.1	

Data are presented as *n* (%) or mean ± standard deviation (median)

SC secondary cancer, *CRT* cranial irradiation, *AML* acute myeloid leukemia, *MDS* myelodysplastic syndrome, *ALL* acute lymphoblastic leukemia, *NHL* non-Hodgkin lymphoma, *PNET* primitive neuroectodermal tumor, *GI* gastrointestinal, *DOX* doxorubicine, *CI* confidence interval

Kaplan–Meier OS curves for patients with secondary cancers are shown in Fig. 3c. All patients with secondary thyroid cancer survived during the follow-up period. The lowest survival probabilities by log-rank test were observed for patients with hematological malignancies compared to patients with brain tumors or adult-type carcinomas ($p = 0.045$). Patients who developed within the 5-year period showed worse prognosis than those who developed secondary cancer in the 5-year period or later ($p < 0.001$, Fig. 3d).

SIR and AER

SIRs based on the general population from the regional cancer registration database of the National Cancer Center Hospital in Japan [17] are shown in Table 2 and, collectively, represent a 12.1-fold (95 % CI 10.1–14.4) increased risk of all secondary cancers during a total of 77,151 person-years of observation. The total AER for secondary cancers was 306 per 100,000 person-years.

Risk factors for secondary cancers

Although competing-risk analyses comparing patients with secondary cancers showed significant differences among primary cancer classifications (Fig. 4a), no statistically significant difference with regard to age at primary cancer diagnosis was observed (Fig. 4b). Therapy-associated risk factors were identified in patients receiving surgery (Fig. 4c), radiotherapy (Fig. 4d), or SCT for primary cancers (Fig. 4e, f) by the Gray method. The cumulative incidence of secondary cancer for the irradiated group continued to increase with time even at >20 years after primary cancer diagnosis, while the incidence in the non-irradiated group remained constant after approximately 15 years (Fig. 4d).

Univariate analyses (crude HR) comparing patients with and without secondary cancers showed no statistically significant relationship with regard to sex or age at primary cancer diagnosis (Table 3). However, the distribution of some of the primary cancers and the attained age at last follow-up demonstrated significant relationships with the development of a secondary cancer. With multivariate Cox regression analysis (Table 3), significant risk factors for secondary cancers were age at primary cancer diagnosis (3–6 years; HR 1.92; 95 % CI 1.16–3.16; $p = 0.011$ and ≥7 years; HR 3.10; 95 % CI 1.79–5.36; $p < 0.001$), retinoblastoma as the primary cancer (HR 3.81; 95 % CI 1.53–9.47; $p = 0.004$), bone/soft tissue sarcomas as the primary cancer (HR 2.78; 95 % CI 1.44–5.38; $p = 0.002$), attained age (≤9 years; HR 7.86; 95 % CI 3.85–16.1; $p < 0.001$ and 9.01–16.00 years; HR 3.63; 95 % CI 2.16–6.09; $p < 0.001$), and allogeneic stem cell transplantation (HR 1.81; 95 % CI 1.16–2.83; $p = 0.010$).

Discussion

To the best of our knowledge, this is the first report from an Asian country to describe the epidemiology of secondary cancers in all kinds of childhood cancer survivors [20]. We found that the cumulative incidence rate of secondary cancers was 1.1 % (95 % CI 0.9–1.4) at 10 years and 2.6 % (95 % CI 2.1–3.3) at 20 years after primary cancer diagnosis. We also observed no marked difference in the cumulative incidence between 2-month and 5-year survivors

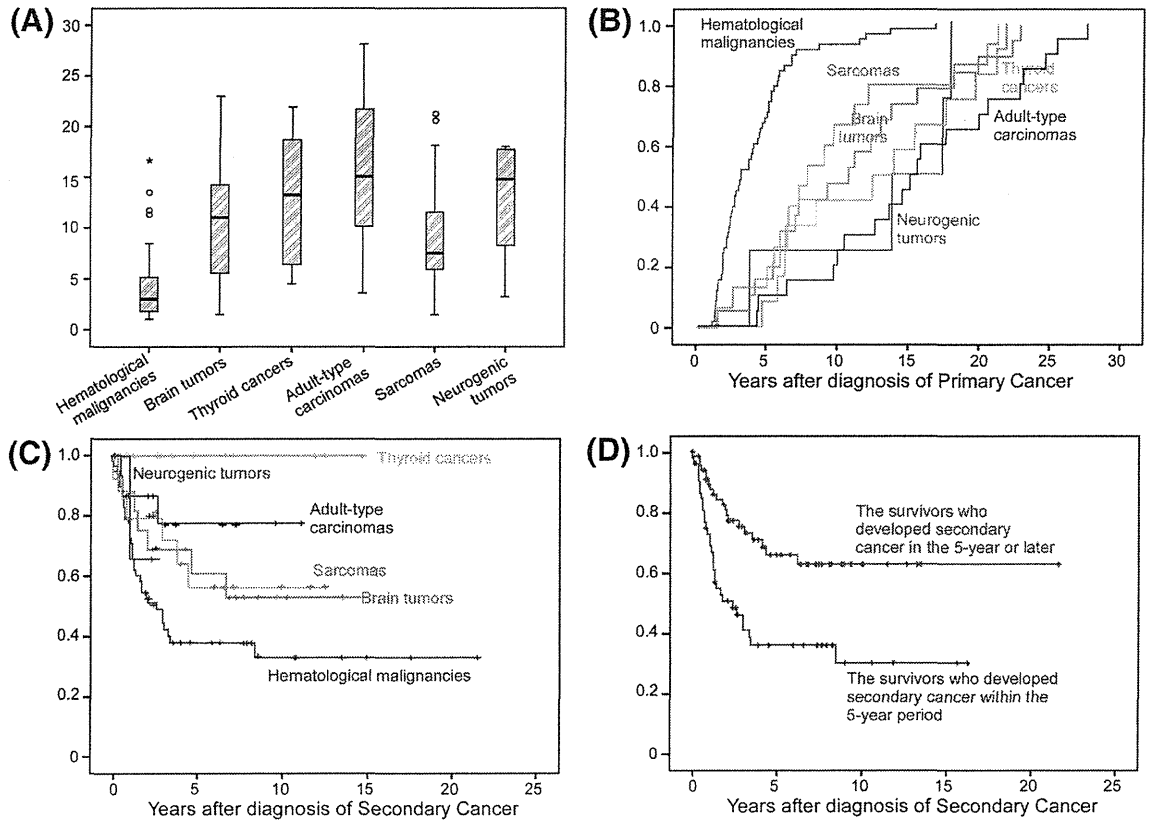

Fig. 3 Cumulative incidence of secondary cancers and clinical characteristics according to the type of secondary cancer (2-month survivors) **a** *Box* and *whisker* plots of the incubation time from primary cancer diagnosis to the development of secondary cancer. The *boxes* represent the first and third quartiles, and the *thick band* represents the median. The ends of the *whiskers* represent the minimum and maximum of all data within 1.5 × the interquartile range from the *bottom* or *top* of the *box*. The *circles* represent outliers. The median time was shortest for hematological malignancies, followed by those for sarcomas and brain tumors. **b** Kaplan–Meier curves of the cumulative proportion of secondary cancers according to secondary cancer types ($p < 0.001$, log-rank test). **c** Kaplan–Meier survival curves for overall survival of secondary cancer patients. The survival probabilities were lowest for patients with hematological cancers. Actual survival at 10 years after secondary cancer diagnosis depended on the cancer type—thyroid cancers (100 %), adult-type carcinoma (61 %), brain tumors (53 %), sarcomas (46 %) and hematological malignancies (29 %) ($p = 0.005$, log-rank test). **d** Patients who developed within the 5-year period showed worse prognosis than those who developed secondary cancer in the 5-year period or later ($p < 0.001$)

regardless of whether or not cases who developed secondary cancer within 5 years were included.

The risk of secondary cancers in childhood cancer survivors may be influenced by genetic predisposition [21, 22]; however, growing evidence indicates that other major contributing factors may be the type of primary cancer and associated therapy [23–25]. The survival probability for a given treatment should be considered when interpreting the risk of developing secondary cancers because low survival will result in fewer reported secondary cancers. Although the lifetime incidence of secondary cancers has not yet been defined, previous studies conducted in the USA and Europe have estimated it to be between 2 and 5 % within the first 20 years of the initial primary cancer diagnosis. [7–9].

The majority of secondary AML and MDS cases develop within 5 years after primary cancer diagnosis, as reported previously [8, 14, 15] and in the present study. Comparatively, the cumulative incidence and SIR estimates of AML and MDS as secondary cancers reported in the CCSS and BCCSS were lower [3, 9, 11]; however, this might be explained by the inclusion of only childhood cancer patients that survived at least 5 years. The distribution of secondary cancer classifications in previous representative reports on secondary cancers are shown in Supplemental Fig. 2 with comparison between all/2-month survivors and 5-year survivors. In studies comparing 5-year survivors with 2-month survivors, the proportions of hematological malignancies were relatively low, while those of skin cancers were high. Of note was that there were no skin cancers as secondary cancers in this study, which might partly explain the low incidence of secondary cancers in Japan.

Our results were consistent with previous studies with respect to median incubation time by secondary cancer

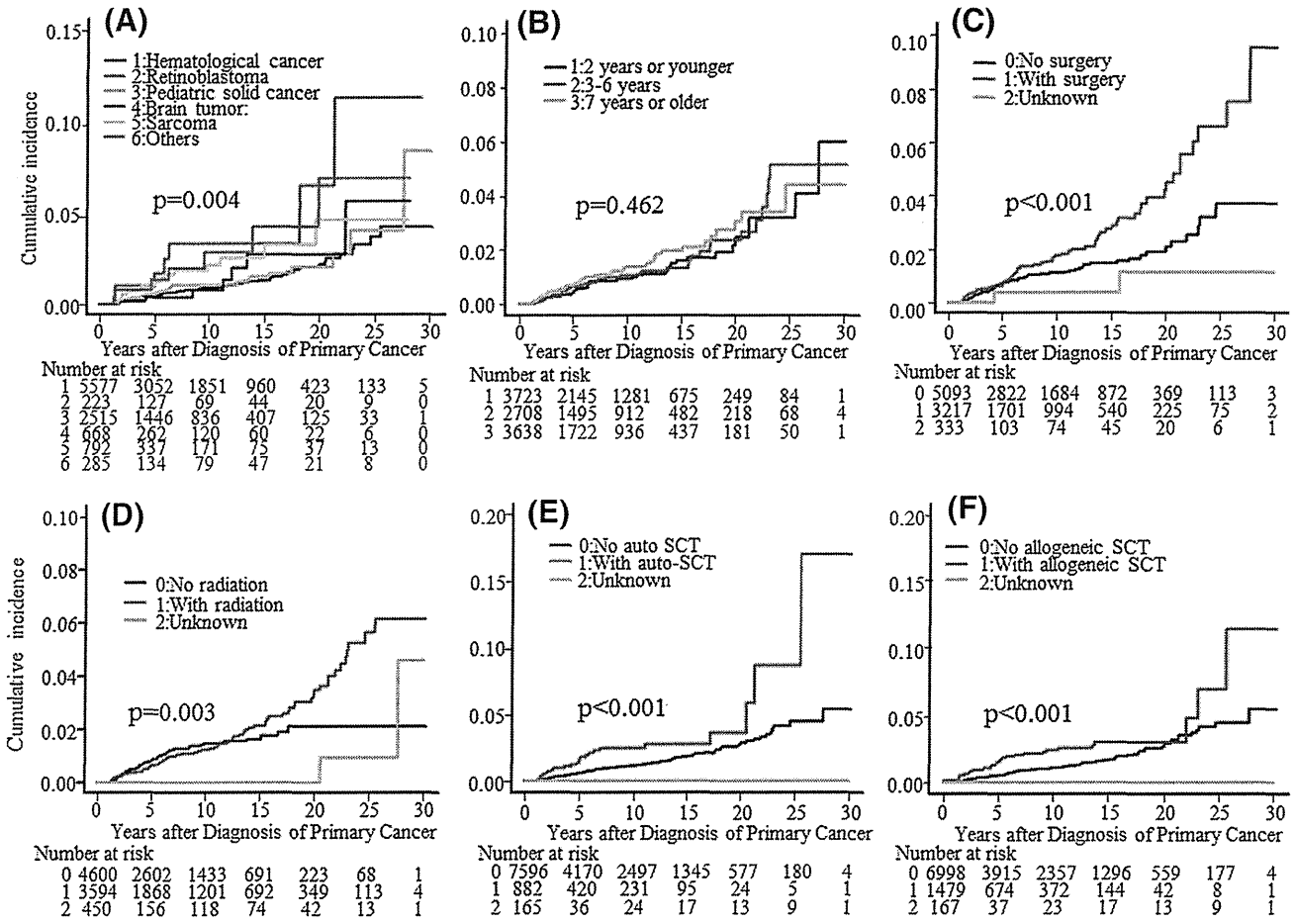

Fig. 4 Cumulative incidence of secondary cancers in pediatric cancer patients (2-month survivors). The cumulative incidence of secondary cancers as a function of time after the primary cancer diagnosis over a maximum follow-up of 30 years, analyzed using the Gray method: **a** primary cancer diagnostic groups, **b** age at primary cancer diagnosis, **c** surgery, **d** radiation, **e** autologous stem cell transplantation (SCT), and **f** allogeneic SCT. The cumulative incidence depended on the type of primary cancer ($p = 0.004$). The risk for secondary cancers was highest in patients with retinoblastoma followed by cancer of 'other' types. Competing-risk analyses for secondary cancers showed no statistically significant difference with regard to age at primary cancer diagnosis (**b**). Therapy-associated risk factors were identified in patients receiving surgery (**c**), radiotherapy (**d**), or SCT for primary cancers (**e**, **f**)

type (shortest for hematological malignancies followed by bone/soft-tissue sarcomas), [8, 14, 15] sarcoma predominance in retinoblastoma, [26] over-representation of girls in secondary thyroid cancers [27], and radiation as a strong risk factor for the development of secondary brain tumors [28] and thyroid cancers [27]. The prognoses after secondary thyroid cancer and adult-type carcinoma were relatively good (Fig. 3c), [15, 20] suggesting that detection of these secondary cancers does not mean disappointing results for childhood cancer survivors if they receive only timely treatments. At the same time, considering the poor prognosis of secondary hematological malignancies (Fig. 3c), it is important to identify the associated factors and minimize the development of secondary hematological malignancies. Of note, the cumulative incidence of secondary cancers for the irradiated group continued to increase with time, even >20 years after primary cancer diagnosis, suggesting a long-term effect of irradiation on the development of secondary cancers (Fig. 4d). Furthermore, we identified allogeneic SCT as a strong therapeutic risk factor of secondary cancers [29, 30].

Lastly, we detected that HRs for retinoblastoma and bone/soft tissue sarcomas were significantly associated with secondary cancer after adjusting for age and therapeutic factors, supporting the findings by Guerin et al. [24] that indicated a significantly increased risk of developing any secondary cancer following Hodgkin's lymphoma, retinoblastoma, malignant bone tumor, soft tissue sarcoma, or germ cell tumor as primary cancers, after adjustment for chemotherapy and family cancer syndrome.

The large sample size and 2-month survivors in the current study should be considered a strength. As a result, we were able to evaluate the cumulative incidence/SIR and explore the risk factors associated with secondary cancers

Table 3 Cox-regression analysis evaluating the association between select characteristics of primary cancer diagnosis and the risk of developing secondary cancer

	Patients with secondary cancer	Patients without secondary cancer	Crude HR (95 %CI)	Adjusted HR (95 %CI)	*p* value
Sex					
Male	66	5,642	Reference	Reference	
Female	62	4,299	1.20 (0.85–1.69)	1.15 (0.81–1.63)	0.443
Age at cancer diagnosis					
≤2 years	42	3,681	Reference	Reference	
3–6 years	37	2,671	1.21 (0.78–1.88)	1.92 (1.16–3.16)	0.011
≥7 years	49	3,589	1.51 (0.99–2.28)	3.10 (1.79–5.36)	<0.001
Primary cancer					
Hematological cancer	63	5,514	Reference	Reference	
Retinoblastoma	7	216	2.58 (1.18–5.63)	3.81 (1.53–9.47)	0.004
Pediatric solid cancer	28	2,487	1.03 (0.66–1.61)	1.44 (0.80–2.60)	0.226
Brain tumor	7	661	1.45 (0.66–3.17)	1.86 (0.80–4.33)	0.148
Bone/soft tissue sarcoma	15	777	2.30 (1.31–4.04)	2.78 (1.44–5.38)	0.002
Others	7	278	2.37 (1.09–5.18)	3.33 (1.44–7.68)	0.005
Age at last follow-up					
≤9 years	7	3,320	3.37 (1.87–6.07)	7.86 (3.85–16.1)	<0.001
9.01–16 years	20	3,256	2.32 (1.46–3.68)	3.63 (2.16–6.09)	<0.001
>16 years	10	3,456	Reference	Reference	
Therapy					
Radiation	73	3,521	1.22 (0.91–1.63)	1.12 (0.81–1.63)	0.527
Surgery	65	3,152	1.44 (1.08–1.94)	1.05 (0.70–1.59)	0.803
Allogeneic stem cell transplantation	33	1,446	1.66 (1.17–2.34)	1.81 (1.16–2.83)	0.010
Autologous stem cell transplantation	23	859	1.60 (1.09–2.34)	0.94 (0.58–1.53)	0.793

HR hazard ratio, *CI* confidence interval

in this cohort. Hematological secondary malignancies with worst prognosis were under-represented in the analysis of only 5-year survivors. Risk factor analyses in only 5-year survivors are not sufficient. Second, the sample, which was obtained from hospitals distributed nationwide from Hokkaido to Kyushu in Japan, is likely to be representative of Japanese childhood cancer survivors.

Our study has certain limitations. The study population was hospital-based (not population-based); therefore, external validation may be required to extend our results to all Japanese childhood cancer survivors. There is also a possibility that the number of patients with secondary cancers was under-estimated because of loss to follow-up. The proportion of patients with hematological malignancies is almost 50 % in this cohort, which is higher than the reported incidence of pediatric hematological malignancies among pediatric cancer (30–40 %). This may also contribute to the lower incidence of secondary cancer in this cohort. The follow-up duration was relatively short (median 8.4 years) in this study compared to studies conducted in the USA and Europe. To address this concern, we conducted a sensitivity analysis using 5-year survivors that included only patients who had survived >5 years after primary cancer diagnosis. These results were consistent with the primary analyses regardless of whether or not cases who developed secondary cancer within 5 years were included.

In conclusion, the cumulative incidence of secondary cancers after a primary cancer diagnosis is relatively low compared to previous reports, although still 12 times higher than in the general population. Efforts to identify the causative carcinogenic factors should continue, and future treatment protocols should take these factors into account to maximize the chances of a long and healthy life, while preserving the efficacy of cancer treatment.

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Center, National Center for Child Health and Development, Tokyo, Japan. (5) Hematology and Oncology, Shizuoka Children's Hospital, Shizuoka, Japan. (6) Pediatrics, Niigata Cancer Center, Niigata, Japan. (7) Pediatrics, Mie University Graduate School of Medicine, Mie, Japan. (8) Hematology/Oncology, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan. (9) Pediatrics, Hiroshima University Hospital, Hiroshima, Japan. (10) Pediatrics, National Kyushu Cancer Center, Fukuoka, Japan. (11) Pediatrics, Kurume University School of Medicine, Kurume, Japan. (12) Pediatrics, Nippon Medical School, Tokyo, Japan. (13) Hematology, Kanagawa Children's Medical Center, Yokohama, Japan. (14) Pediatrics, Sapporo Hokuyu Hospital, Sapporo, Japan. (15) Pediatrics, Kyoto University School of Medicine, Kyoto, Japan.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Original Article

Support for school reentry and relationships between children with cancer, peers, and teachers

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Abstract ***Background:*** Returning to school after a cancer diagnosis can be socially challenging for children with cancer. This study investigated the form of support for school reentry and the associations with social support from peers and teachers.

Methods: This was a multicenter cross-sectional study. Children with cancer and their guardians completed questionnaires. Their guardians also underwent a semi-structured interview to describe the background of support for school reentry.

Results: Thirty-nine children with cancer and guardian dyads completed questionnaires and three guardians underwent semi-structured interview. Peer visits and their understanding of hospital experiences and how to interact with children were related to social support from peers. Teachers' understanding of physical appearance, academic performance, hospital experience and of how to interact with children was related to social support from peers. Teachers' understanding of diagnosis/treatment, academic performance and their status as the liaison between doctors/nurses in hospitals and teachers in local schools were also related to social support from teachers. Furthermore, children with cancer were also encouraged to establish supportive relationships with peers and teachers as a result of school reentry support that (i) helped children to feel that they are still members of the local school; (ii) improved peer and teacher understanding of the long-term recovery process of children with cancer; and (iii) facilitated the children's own awareness that they are fighting the disease.

Conclusions: The multidisciplinary team consisting of the children with cancer, their families, doctors, nurses and teachers in the local school need to communicate with peers regarding positive experiences of fighting, and overcoming, severe disease.

Key words adolescent, child, interpersonal relationship, neoplasm, school.

The incidence of childhood cancer in Japan is 103.7 per million for boys and 80.1 per million for girls.[1] Children with newly diagnosed cancer are in the hospital for 6–12 months and attend the outpatient clinic for 12–24 months.[2] In Japan, children with illness including cancer are educated in hospital schools during hospitalization and their school registers must be transferred from local schools to hospital schools. They also return to school after discharge and their school registers must also be transferred from hospital schools to local schools.[3] Returning to school after cancer diagnosis can often be socially challenging for children with cancer because treatment modalities could affect integration into daily life.[4] Use of a multidisciplinary team that includes doctors and nurses as well as school personnel, is crucial in supporting school reentry.[5,6]

Support for school reentry has focused on staying in contact with peers and teachers during hospitalization and providing information to peers and teachers. Both of these forms of support are often provided in Japan.[3] Children with cancer require long-term hospitalization for treatment and are not registered in local schools for a long time. Therefore, medical staff should encourage peers and teachers in the local schools to stay in contact with hospitalized children with cancer. This contact helps children with cancer to feel that they are still part of the class.[7] Peers and teachers also are presented with diagnosis- and treatment-specific information, such as on the effects of the disease and treatment, and the way in which the peers and teachers can assist children with cancer.[7,8] When presented with accurate information, peers and teachers can become the patients' main source of support.[9,10]

Support for school reentry are effective in increasing illness-specific knowledge and positive attitudes towards children with chronic illness.[8,11] The attitude towards children with chronic illness, however, has been measured using peer or teacher report, and this is insufficient in appropriately reflecting the relationships between children with chronic illness, peers, and teachers.[11]

Social support offered peer and teacher relationships is important, especially for children with cancer. Most children with cancer are relatively well adjusted to living with cancer, but some children

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are at increased risk of potential physical and psychosocial problems that require support from significant others, compared with the general population.[12] Children with cancer require social support arising from supportive relationships with peers and teachers after school reentry,[13] although teachers in the hospital schools play a vital role in managing study in hospitals. Children with cancer also looked on peers as a particularly important source of emotional support and companionship, although their family were mentioned more often and provided support in a more tangible way, such as through medical treatment.[14] Children with cancer need available support from significant others in order to adjust to living with cancer.[13] For children with cancer, however, there has been no study on the association between support for school reentry and social support via supportive relationships with peers and teachers. Previous research has suggested that social support is related to age at study period, gender, and trait anxiety.[15] Age at study period, gender, and trait anxiety should be controlled to clarify the association between support for school reentry and social support.

The aim of this preliminary study was therefore to clarify the association between support for school reentry and relationships with peers and teachers. We suggest that school reentry support consists of two major dimensions: (i) maintenance of contact with peers and teachers; and (ii) provision of information about cancer to peers and teachers. Furthermore, we posit that supportive relationships with peers and teachers would be characterized by high social support.

Methods

Subjects

Children with cancer aged 9–18 years who were an outpatient at three hospitals in Japan between September 2012 and March 2013, and their guardians, were eligible for the study. Inclusion criteria were (i) age between 9 and 18 years (according to the age at which children themselves can complete questionnaires, and at which relationships with peers and teachers are important for daily life); (ii) age <15 years old at diagnosis of cancer (due to the age definition of childhood cancer);[16] (iii) ≤3 years elapsed since discharge (to enable investigation of supportive relationships with peers and teachers established at the beginning of school reentry that help them to adjust to their school life later), and (iv) currently enrolled in a regular class (because most children with cancer return to regular classes and because the relationships with peers and teachers in regular class could differ from those in special support classes). Exclusion criteria were (i) relapse at any time before the study period; (ii) primary or metastatic brain tumor; and (iii) being otherwise ineligible for participation (e.g., mental disorder). Children diagnosed with brain tumor were excluded because of a higher probability of learning disability, cognitive disability, or physical disability related to their illness.[17,18]

Study design and procedure

This multicenter study was cross-sectional in design and used questionnaires and interviews.

When children with cancer and their guardians visited the study hospitals, the researchers informed them of the questionnaire study. A total of 62 child with cancer and guardian dyads were given the questionnaires by the researchers after consenting to participate in the study. Children with cancer and their guardians completed separate questionnaires (Table 1). The questionnaire for children with cancer consisted of items on social support and trait anxiety. The questionnaire for the guardians consisted of items on demographic and medical information and support for school reentry. Guardians answered the items about school reentry support because they understand about school reentry support more than children with cancer and because it was both methodologically and ethically difficult to ask peers and teachers about support for school reentry directly.

Twelve guardians at one of the three hospitals were also informed of the interview study. After completing the questionnaire, the guardians underwent semi-structured interview to describe the background of support for school reentry, such as the need for support for reentry. Interviews were recorded with an recorder and interview data were transcribed verbatim.

This study was approved by the board of ethics of the institution the researcher belong to and all study hospitals.

Dependent variables

Social support

Children with cancer evaluated social support. The Scale of Expectancy for Social Support (SESS) was used, which measures availability of support from mothers, fathers, siblings, peers, and teachers to handle future problems.[19] The scale evaluates social support from each source separately with 16 items rated on a 4-point scale (1, never; 4, very much), and total scores for each subscale can range from 16 to 64. The reliability and validity of the SESS have been confirmed. Higher SESS scores indicate that individuals have greater availability of support. We used only the subscales for peers and teachers in this study. Cronbach α coefficients of the subscales were 0.96–0.97.

Independent variables

Demographic and medical information

Guardians were asked about demographic and medical information of both children with cancer and guardians. The demographic and medical information of children with cancer were as follows: age at study period, gender, diagnosis, treatment protocol, age at diagnosis, time since discharge, receiving outpatient treatment, frequency of school absence and number of class changes and change ups (e.g. a move from elementary to middle school) during hospitalization/after discharge. Guardian demographics included age at study period, gender, and relationship to children with cancer.

Children with cancer evaluated trait anxiety. Trait anxiety (i.e. a tendency to react with anxiety to potentially uncomfortable experiences) was evaluated using the trait anxiety subscale of the

Table 1 Questionnaire survey items and respondents

Items	Respondents
Social support	Children with cancer
Demographic and medical information	Guardians (children with cancer completed only trait anxiety)
School reentry support	Guardians

State–Trait Anxiety Inventory for Children (STAIC-t).[20] This 20-item instrument has confirmed reliability and validity. STAIC-t uses 3-point Likert scales (1, hardly ever; 3, often). The total score ranges from 20 to 60 with higher scores indicating higher trait anxiety. The Cronbach's α coefficient was 0.91 in this study.

School reentry support

Scale development: We devised the items on support for school reentry. First, the specific and vital items on support for school reentry in children with cancer were extracted from previous research in Japan.[3,21] Second, pediatricians who examine children with cancer, researchers in the area of pediatric nursing and researchers in the area of education for children with chronic illness or disability discussed the content of the scale on support for school reentry to confirm the content validity of this scale. Cronbach's α coefficients were also calculated to confirm the internal consistency of this scale. School reentry support scale measured guardian perception of support for school reentry.

Staying in contact with peers and teachers: Staying in contact with peers and teachers consisted of eight categories: "hospital visit by peers", "hospital visit by teachers", "home visit by peers", "home visit by teachers", "treating children as a school member", "sending cards and messages", "sending school assignments", and "informing peers of children's condition". Guardians evaluated each type of contact in terms of frequency: "How frequently was the contact made?" (0, never; 3, often). The Cronbach's α coefficient was 0.92 in the study.

Providing information for peers and teachers: Information provided to peers in the present class of children with cancer fell into 10 categories: 'diagnosis/treatment", "health status/prognosis", "being absent, late for school, and leaving early", "susceptibility to infection", "physical appearance", "academic performance", "children's experience struggling with severe disease in hospital", "how to interact with children", "how to assist children", and "children's perception of cancer". Guardians evaluated all information in terms of peer understanding: "To what extent do peers understand?" (0, do not understand; 3, understand). Information provided to teachers consisted of the same 10 items and one additional item about status as a liaison between doctors/nurses in the hospital and teachers in the local school. All information was evaluated in the same way as that for peers. The Cronbach's α coefficient was 0.96.

Statistical analysis

Data from the questionnaire survey were analyzed using partial correlation analysis to clarify what forms of support for school reentry were related to social support. Partial correlation coefficients between SESS and each form of support for school reentry were calculated controlling for demographic and medical variables considered as covariates to support for school reentry and perceived social support (age at study period, gender, trait anxiety, receiving outpatient treatment, and entering higher-grade schools after discharge). Data were analyzed using SPSS 12.0J for Windows (SPSS, Chicago, IL, USA). Two tailed $P < 0.05$ was considered statistically significant.

Interview data were analyzed using the continuous comparative method.[22] First, the researcher read transcripts repeatedly and comprehended the content and flow of these transcripts. Second, the researcher identified passages containing analytic themes and used these passages as concrete examples in order to create concepts. The researcher then interpreted concepts by looking for opposite and similar examples. Finally, the researcher considered the mutual association between concepts and created categories. The researcher was supervised by professionals in the area of qualitative research throughout this interview survey.

Results

Participants

Thirty-nine dyad questionnaires were returned (response rate, 62.9%), but only data from 36 dyads were included in analysis because two dyads were missing SESS data, and the child in one dyad was diagnosed with aplastic anemia. Three of 12 guardians also consented to being interviewed after completing the questionnaire. The interviews lasted between 42 and 72 min.

Demographic and medical information for participants were as follows: children with cancer were a mean of 13.3 years old at study period, 10.2 years old at diagnosis, and were followed up for a mean of 1.6 years after discharge (Table 2). Fifteen children with cancer (42%) were diagnosed with leukemia, and 23 children with cancer (64%) had received treatment at outpatient clinic.

Table 2 Children with cancer: Demographic and medical characteristics

Total, n = 36	n	%	Mean	SD
Age at study period (years)			13.3	2.1
Gender				
Female	18	50		
Diagnosis				
Leukemia	15	42		
Lymphoma	14	39		
Osteosarcoma	4	11		
Other[†]	3	8		
Treatment protocol[‡]				
Chemotherapy	36	100		
Radiotherapy	11	31		
Surgery	9	25		
Stem cell transplantation	6	17		
Age at diagnosis (years)			10.2	2.8
Time since discharge (years)			1.6	1.1
Receiving outpatient treatment	23	64		
School absence (days)[§]			1.8	5.5
Entering higher-grade schools				
During hospitalization	3	8		
After discharge	19	53		
Class changes				
During hospitalization	26	72		
After discharge	27	75		
Trait Anxiety (STAIC-t)			36.1	8.7

[†]Wilms tumor, ovarian tumor, and nasopharyngeal carcinoma. [‡]Multiple answers allowed. [§]No. days absent in the past month. STAIC-t, Trait anxiety subscale of the State–Trait Anxiety Inventory for Child.

Questionnaire survey

Support for school reentry

Treating children as members of the local school was implemented most often, followed by the sending of cards and messages (Fig. 1). While peers best understood information about susceptibility to infection, teachers best understood information about being absent, late for school, and leaving early (Fig. 2). Teachers also better understood all provided information than peers.

Support for school reentry and social support

Table 3 showed associations between SESS and support for school reentry. According to partial correlation analysis, home visit by peers during temporary discharge was significantly related to social support from peers ($r=0.384$).

Peer understanding of hospital experiences ($r=0.376$) and how to interact with children ($r=0.471$) were positively significantly associated with social support from peers. Teachers' understanding of physical appearance ($r=0.453$); academic performance ($r=0.466$); hospital experience ($r=0.422$); and how to interact with children ($r=0.417$) was related to social support from peers. Furthermore, teachers' understanding of diagnosis/treatment ($r=0.386$); academic performance ($r=0.439$); and their own status as liaisons between hospitals and schools ($r=0.422$) were related to social support from teachers.

Interview survey

Children's recognition that they are still members of the local school

The interview survey found that it was important to make children with cancer recognize that they were members of the local school while staying in contact with peers and teachers. Children with cancer were transferred to the hospital school during hospitalization, where they often felt lonely because they were unable to experience life with peers at their local school. They also had severe physical and psychological stress resulting from disease and treatment, making it difficult for them to think of school reentry. They stayed in contact with peers and teachers, however, and were still recognized as members of the local school. This recognition encouraged children with cancer to establish new relationships with peers and teachers after discharge.

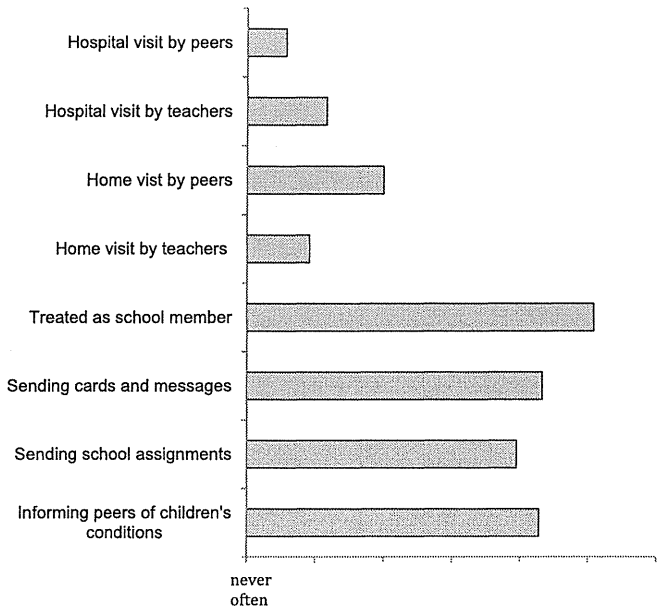

Fig. 1 Contact frequency with peers and teachers ($n=36$).

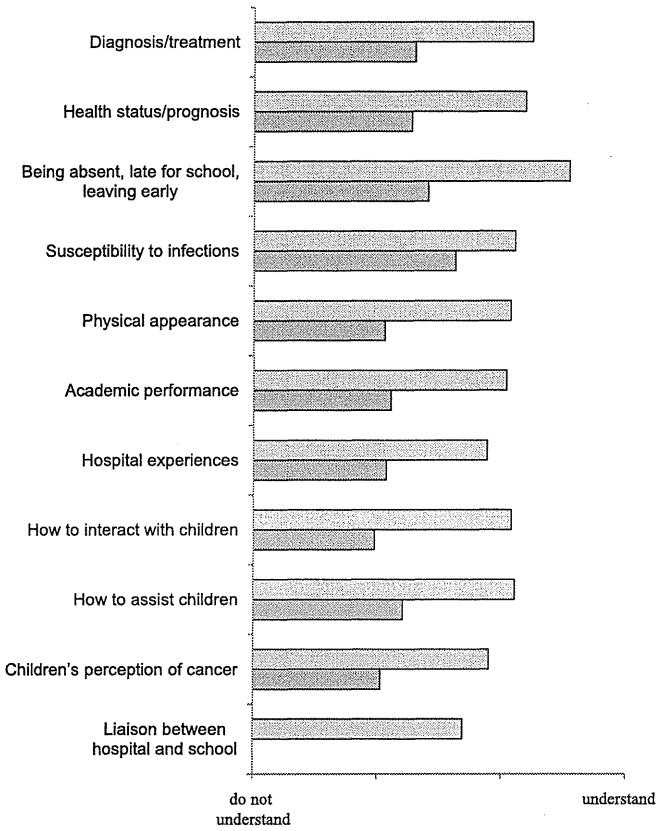

Fig. 2 (▒) Peer and (▒) teacher understanding ($n=36$).

> *The teacher in the local school repeatedly said that [my daughter] would return to the local school someday... it made [my daughter] feel that she had a place to return to. That thought encouraged her.*

Peer and teacher understanding of the long-term recovery process

In the interviews, guardians said it was important that peers and teachers understood the long-term recovery process of children with cancer while providing them with information. Children with cancer experienced difficulties related to cancer and its treatment in their school lives when returning to school. Furthermore, peers and teachers were troubled in how to deal with children with cancer. Providing appropriate information to peers and teachers encouraged them to understand the long-term recovery process of children with cancer since the diagnosis. This type of understanding enabled peers and teachers to deal with children with cancer in a more appropriate way.

Table 3 Associations between SESS and support for school reentry (n = 36)

	SESS (peers)		SESS (teachers)	
	$r^{\dagger}$	*P*-value	$r^{\dagger}$	*P*-value
Contact frequency with peers and teachers				
Hospital visit by peers	0.049	0.794	–0.042	0.821
Hospital visit by teachers	–0.207	0.265	–0.259	0.159
Home visit by peers	**0.384**	**0.033**	0.301	0.100
Home visit by teachers	0.287	0.118	0.100	0.594
Treating children as school member	–0.123	0.511	0.112	0.549
Sending cards and messages	–0.067	0.721	0.170	0.360
Sending school assignments	–0.243	0.188	–0.150	0.421
Informing peers of children's conditions	–0.117	0.533	0.060	0.748
Peers' understanding				
Diagnosis/treatment	0.270	0.142	0.069	0.711
Health status/prognosis	0.288	0.116	0.060	0.749
Being absent, late for school, and leaving early	0.167	0.369	0.171	0.358
Susceptibility to infection	0.311	0.088	0.028	0.880
Physical appearance	0.251	0.173	–0.046	0.804
Academic performance	0.304	0.097	0.013	0.946
Hospital experiences	**0.371**	**0.040**	0.270	0.141
How to interact with children	**0.474**	**0.007**	0.293	0.110
How to assist children	**0.365**	**0.044**	0.209	0.260
Children's perception of cancer	0.289	0.115	0.007	0.971
Teachers' understanding				
Diagnosis/treatment	0.322	0.077	**0.386**	**0.032**
Health status/prognosis	0.272	0.139	0.333	0.067
Being absent, late for school, and leaving early	0.266	0.149	0.142	0.446
Susceptibility to infection	0.202	0.276	0.194	0.296
Physical appearance	**0.453**	**0.011**	0.232	0.210
Academic performance	**0.466**	**0.008**	**0.439**	**0.013**
Hospital experiences	**0.422**	**0.018**	0.352	0.052
How to interact with children	**0.417**	**0.019**	0.231	0.212
How to assist children	0.306	0.094	0.180	0.333
Children's perception of cancer	0.354	0.051	0.274	0.135
Liaison between hospital and school	0.354	0.051	**0.422**	**0.018**

†Partial correlation coefficient. Variables controlled for in partial correlation analysis were as follows: age at study period, gender (male, 1; female, 0), receiving outpatient treatment (receiving, 1; not receiving, 0); entering higher-grade schools after discharge (entering, 1; not entering, 0) and trait anxiety. Pearson product–moment correlation coefficients between SESS (peers) and controlled variables: age at study period, $r = 0.19$ ($P = 0.27$); gender, $r = -0.25$ ($P = 0.14$); receiving outpatient treatment, $r = 0.09$ ($P = 0.60$); entering higher-grade school after discharge, $r = 0.20$ ($P = 0.23$); and trait anxiety, $r = -0.40$ ($P = 0.02$). Pearson product–moment correlation coefficients between SESS (teachers) and controlled variables: age at study period, $r = -0.07$; $P(= 0.69)$, gender, $r = -0.07$ ($P = 0.68$); receiving outpatient treatment, $r = 0.17$ ($P = 0.33$); entering higher-grade school after discharge, $r = 0.04$ ($P = 0.82$); and trait anxiety, $r = -0.39$ ($P = 0.02$). SESS, Scale of Expectancy for Social Support.

She couldn't understand some things in the class, because she hadn't been able to study during hospitalization...her friendship after school reentry was influenced by just her friendship during hospitalization.

I said to her that she should be proud of herself because she had been hanging on, which was proof that she'd done her best. Although she has deep scars in her foot, I want her to feel that she didn't need to be ashamed of the scars. That's what I said to the teacher.

Children's own awareness that they are fighting the disease

The guardians also reported in the interviews that providing the information made children with cancer aware of their own fight with the disease. As much as possible, children with cancer wanted to hide any physical changes in their appearance associated with the disease and treatment from their peers and teachers. Guardians also understood how they viewed the changes in their physical appearance. In contrast, guardians hoped that children with cancer would begin to regard these changes as proof of fighting their disease by providing information for peers and teachers. As a result, children with cancer experienced a positive school life because of this proof.

Discussion

This study found that home visits by peers and their understanding of children with cancer were associated with social support from peers. Given increased teacher understanding of children with cancer, children with cancer received social support from teachers. Children with cancer were also encouraged to establish supportive relationships with peers and teachers, when school reentry support (i) helped children to realize that they are still members of the local school, (ii) improved peer and teacher understanding of the long-term recovery process of children with

cancer; and (iii) facilitated the children's own awareness that they are fighting the disease.

Face-to-face contact with peers reduced concerns that children with cancer were teased when they returned to school.[6] That study suggested that particularly home visit by peers reduced the concerns of children with cancer and helped them to maintain a supportive relationship with peers. Children with cancer also could meet their peers and teachers face to face more easily during temporary discharge than during hospitalization because their health conditions were stable. Previous research suggested that staying in contact with peers and teachers reduced the concerns of children with cancer about peer rejection or ridicule.[9] In addition to the finding from previous research, the present study found that staying in contact with peers and teachers made children with cancer recognize that they were members of their local school. This recognition was a source of strength for coping with more intensive medical treatment;[21] therefore, support for school reentry is important for coping with stressful events in the hospital.

Peer understanding of how to interact with and assist children with cancer was related to social support from peers. Teachers' understanding of diagnosis/treatment, academic performance and of their own status as liaisons between hospitals and schools was related to social support from teachers. This suggests that in order to develop supportive relationships, it is vital that peers have an understanding of school life for children with cancer and that teachers have an understanding of the medical and academic information involved, as well as of the cooperation needed between hospital and school.

This study found an association between social support from peers and peers' and teachers' understanding of information about how to interact with children with cancer. In children with chronic conditions such as asthma and cerebral palsy, parents and teachers also communicated about how to interact with children with chronic conditions, and this communication contributed to supportive relationships with peers.[23–25] Peers often do not know what to say or how to act around children with cancer and may wait for cues from medical staff or teachers.[10] When peers may become overly nice or doting, children with cancer also perceive this behavior as negatively as they might view teasing. Therefore, doctors, nurses or teachers in the local school who understand the condition of the children and its impact on school life should present peers with accurate information at an age-appropriate level and give them the opportunity to ask any questions.

Information that helped peers and teachers understand the long-term recovery process of children with cancer effectively contributed to social support from peers and teachers. It was noted that physical and psychosocial problems related to cancer and its treatment may hamper children with cancer in adjusting to their school environment.[26] The present study found that it was not sufficient to provide information for peers and teachers regarding only one time point in order to help them to understand the problems involved. They must have an understanding of the long-term recovery process, which would then enable them to place the children's present difficulties at school into perspective.

Peers' and teachers' understanding of hospital experiences of children with cancer was related to social support from peers. When cancer survivors recognize their cancer experiences as positive, their experiences enhance their own confidence in dealing with negative life events after treatment.[27] Children with cancer had overcome severe disease in the hospital. Peers understood this positive experience, so that children with cancer could gain confidence in their school life. Guardians also recognized that providing information to peers helped them to see that the children with cancer are fighting their disease, which supports the aforementioned finding. Previous research reported that children with chronic illness, parents, peers and teachers communicated about the conditions of the children and its negative impact on school life.[23–25] The present study indicates that children with cancer, their families, doctors, nurses or teachers in the local school need to communicate with peers about positive experiences of children fighting cancer and overcoming severe disease. It is also important that this communication is implemented via a multidisciplinary team including the children with cancer and their families as well as doctors, nurse and school personnel.[6]

Limitations and future implications

This preliminary study had some limitations. First, generalization of the present findings must be done with caution because the demographic and medical characteristics of the participants were biased. Some children with cancer may not have participated in this study because they could not establish supportive relationships with peers and teachers. The present findings can be applied only to children with cancer who establish supportive relationships. Also, the present participants were young. These findings thus could not be applied to children with cancer who are older than the present participants because the influence of support for school reentry on relationships with teachers and peers may differ developmentally between younger and older age groups. There was a selection bias with regard to the health status of children with cancer because physicians choose participants. Children in this study were diagnosed with leukemia and lymphoma, therefore, the present findings apply mainly to children with leukemia and lymphoma. Second, guardians of children with cancer evaluated peer and teacher understanding, hence the actual level of understanding by peers and teachers was not measured. The evaluation of these understanding by peer or teacher could differ from that by parent. Evaluation of peer and teacher understanding may produce new information on the association between the understanding of children with cancer and relationships with peers and teachers. Third, late effects and treatment intensity were not evaluated because guardians, rather than the doctors, reported medical information. Late effects and treatment intensity could affect school life of children with cancer and should be evaluated in future research. Fourth, this study was cross-sectional in design and did not confirm any causal relationship. Guardians could evaluate support for school reentry positively, because children with cancer established relationships with peers and teachers. Finally, use of partial correlation analysis in this study inflated the risk of type 1 error and may not have led to accurate results.

Conclusions

Home visits by peers were related to perceived social support from peers. Furthermore, peers' and teachers' understanding of children

with cancer is related to social support from peers and teachers, respectively. Children with cancer were encouraged to establish supportive relationships with peers and teachers, when school reentry support (i) facilitated children's recognition that they are still members of the local school; (ii) improved peer and teacher understanding of the long-term recovery process of children with cancer; and (iii) facilitated children's own awareness that they are fighting the disease. The present study suggests that a multidisciplinary team including the children with cancer, their families, doctors, nurses or teachers in the local school need to communicate with peers about the positive experiences involved in fighting with, and overcoming, severe disease.

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■ 特集 トランジション

小児がんの晩期合併症

前田美穂*

はじめに

小児がんは現在70～80%の治癒が認められ，疾病によっては90%以上が治癒する。しかし，治療終了後に治療に関連したり，あるいは原疾患に関連した問題が生じることが徐々に明らかになってきた。これらの治療後に生じる合併症のことを晩期合併症という。2006年にOeffingerら[1]は，小児がんの経験者は治療終了20年後には60%以上でなんらかの晩期合併症を抱えることになり，そのなかにはGrade Ⅲ，Ⅳという重症な状態が30%もあるとの研究結果を発表した。また2013年にはSt. Jude小児病院より，小児がんに罹患した経験をもつ人では治療終了40年後には90%以上でなんらかの障害をもつとの報告がされた[2]。

晩期合併症には，身体的な問題だけでなく，心理的な問題もある。身体的な問題は表に示すが，身体のあらゆる臓器に起こる可能性があり，原疾患の状態，治療中の合併症，治療法や治療期間，使用した抗がん剤の種類と量，放射線照射を受けた部位と照射量，手術を受けた部位や手術方法，造血細胞移植の前処置の種類などによってさまざまである。現在，多くの研究によって晩期合併症と治療との関係はかなり解明されてきている。一方，心理的な問題も大変重要である。抑うつ状態，posttraumatic stress disorder (PTSD)，不登校，

表 身体的合併症

内分泌系への影響	低身長 肥満・やせ 性腺機能障害・不妊 甲状腺機能異常 耐糖能異常	消化器への影響	癒着性イレウス
		腎への影響	腎機能低下
		骨筋肉への影響	大腿骨頭壊死 骨密度低下 側彎
神経系への影響	認知機能障害 知能低下 白質脳症 学習障害 てんかん 運動器異常 末梢神経障害	歯牙の影響	矮小歯 歯根の短縮 歯牙形成異常
		聴力への影響	難聴
		視覚への影響	視力低下
		皮膚への影響	萎縮・色素沈着
呼吸器系への影響	呼吸機能低下	免疫機能低下	
心機能への影響	心筋障害 冠動脈障害	二次性腫瘍	悪性腫瘍 良性腫瘍
肝への影響	輸血によるウイルス性肝炎 肝への鉄沈着		

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パニック障害などのほか，認知力の低下なども報告されている。これらが成人期にどのような影響をもたらすか，その対処はどのようにしたらよいか，小児から成人期への移行医療という観点からも重要な問題と考えられる。本稿では，スペースの関係で身体的問題の一部を解説するにとどまるが，晩期合併症の詳細に関しては成書を参考にしていただきたい。

Ⅰ．身体的合併症

小児がんの治療である化学療法，放射線療法，外科的治療は，いずれも晩期合併症の原因となりうる（ただし，造血細胞移植療法は化学療法と放射線療法に含む）。化学療法に使用する抗がん剤では，主なものでもアルキル化剤の不妊や無月経，アントラサイクリン系薬剤の心毒性，トポイソメラーゼⅡ阻害剤（VP-16など）による二次性白血病，シスプラチンなどの白金製剤による聴力障害や腎障害などがある。また年少時に抗がん剤治療を受けると，歯牙の形成異常がみられることも明らかになっている。

放射線療法では，頭蓋照射であれば成長障害，白質脳症，二次性脳腫瘍など，肺照射では肺の線維化による呼吸機能低下，食道炎，二次性乳がんなど，腹部照射では消化管の異常，軟部組織や骨の萎縮，卵巣機能低下，性ホルモンの異常など，手術では胸郭手術での側彎や，腹部手術による癒着性イレウスなど，さまざまである。本稿では，このなかから比較的多く報告されているもの，生命を脅かす可能性のあるものを中心に解説をする。

1．内分泌合併症

1）成長障害

小児がんの晩期合併症でもっとも多くみられるのは，内分泌障害であるといわれている。以前は小児がんでもっとも頻度の高い急性白血病，とくに急性リンパ性白血病では頭蓋照射が頻繁に行われていたために視床下部や下垂体の機能低下がよくみられていたが，最近白血病の治療では頭蓋照射は少なくなり，また脳腫瘍の治療における頭蓋照射でも以前より照射量の減少などが行われるようになったため，合併症は減少傾向にある。視床下部，下垂体のなかでは，成長ホルモンの分泌に関与するエリアがもっとも放射線の感受性が高いために，成長ホルモンの分泌障害による低身長がほかの内分泌障害より頻度が高いといわれている。とくに5歳以下の低年齢で頭蓋照射を受けた場合のほうが，それ以上で受けた場合より多いといわれている[3]。

2）性腺機能障害

性腺機能については，精巣や卵巣が直接障害を受けた場合と，視床下部や下垂体を介したホルモンの分泌異常が起こる場合がある。また性腺機能に関しては，男子と女子では異なった問題が多いため，それぞれに分けて述べる。

(1) 男子

直接障害のうち，男児では主にアルキル化剤によるものと放射線照射によるもの，また手術で精巣を摘出した場合などがある。アルキル化剤による精細胞の萎縮と線維化が不妊を招くことが知られている。シクロホスファミドの総投与量が7.5 g/m^{2}以上であるとその危険性があるとされているが，投与を受けた年齢にも関係があり，思春期以降のほうが感受性が高く危険度が増すとされている。また，シスプラチンなどの白金製剤でも不妊を呈することがある。

精巣への放射線照射で精子の産生量の低下が指摘されている。2～3 Gyでは1～2カ月で無精子症が起こり，回復するとしても数年後であり，12 Gy以上で恒久的な無精子症になるとの報告がある[4]。Leydig細胞への影響としては，24 Gyの精巣照射でテストステロンの低下と黄体形成ホルモン（LH）の上昇を認めたという報告がある[5]。なお，卵胞刺激ホルモンは主に精細管の障害で上昇し，LHはLeydig細胞の障害で上昇する。治療を受けた年齢との関係としては，放射線照射の場合は低年齢のほうが成人よりLeydig細胞への影響が大きいといわれている。

手術による性腺への直接的な合併症としては，両側後腹膜のリンパ節郭清や骨盤内臓器の摘出に伴ってインポテンツが生じることなどがある。

(2) 女子

女子の場合は，性腺機能の評価は，男子のように精巣を直接測定したりすることは不可能であり，月経の状態などによる間接的な判断によるこ